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Batch production of micron size particles from poly(ethylene glycol) using supercritical CO_2 as a processing solvent

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Abstract

The major advantage of using supercritical carbon dioxide (CO_2) as a solvent in polymer processing is an enhancement in the free volume of a polymer due to dissolved CO_2, which causes a considerable reduction in the viscosity. This allows spraying the polymer melt at low temperatures to produce micron size particles. We have used supercritical CO_2 as a solvent for the generation of particles from poly(ethylene glycol) (PEG) of different molecular weights. Since PEG is a hydrophilic compound, it is a most commonly used polymer for encapsulating a drug. PEG particles with different properties may allow keeping a good control over the release of the drug. It has been possible to produce particles with different size, size distribution, porosity and shape by varying various process parameters such as molecular weight, temperature, pressure and nozzle diameter. A flow and a solidification model have been applied in order to have a theoretical insight into the role of different parameters.

Keywords: PGSS; Supercritical CO_2; Poly(ethylene glycol); Particle; Solidification

1. Introduction

Pharmaceutical industries are always in an utmost need of new technologies, which can produce fine particles without using organic solvents. This is possible with the traditional processes such as grinding or milling. However, the cost in case of cryogenic milling or the heat dissipation during grinding constraint their applications to particular materials. Recently, Beckman (2003) has provided an excellent comparison of the traditional processes with new particle production processes.

During the last two decades, various processes, which use supercritical fluids as solvents or anti solvents have become available. Supercritical fluids could replace the organic solvents due to their gas-like and liquid-like properties, which play a convenient role in the dissolution process. It is possible to produce nano or micron size particles not only for low but also for high molecular weight materials using supercritical fluids (Jung and Perrut, 2001). Among various fluids, carbon dioxide (CO_2) has already been touted as a supercritical fluid for many applications as it is inexpensive and inert in nature. It has a critical temperature close to room temperature (304 K) and a moderate critical pressure (7.38 MPa). Moreover, since it is a gas at ambient conditions, it is easy to separate it from the final product.

PGSS (particles from gas saturated solution) is one of the particle production methods, which uses supercritical fluid as a solvent. PGSS utilizes the solubility of a supercritical fluid in a material. The dissolved supercritical fluid reduces the viscosity of the material to be micronised and hence, allows expansion at low temperatures. The principle of the process is actually very simple. Thermodynamics instability leads to a supersaturation due to reduction in the solubility of a gas when a polymer–gas solution is expanded from a high to a low pressure. The supersaturation results into nucleation of bubbles and a vigorous expansion of these bubbles break up the solution into smaller particles. CO_2 is generally used as a supercritical fluid in PGSS for several polymers mainly due to its high solubility (Weidner et al., 1996, 2000, 2001; Mandel et al., 2001; Liu et al., 2005).

In this work, particle production using supercritical CO_2 from poly(ethylene glycol) (PEG) of different molecular weights has been studied in detail. PEG is one of the commonly used compounds in pharmaceutical industry because of its hydrophilic nature. PEG is available in different states such

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as liquid or solid depending on the molecular weight. In the solid state, PEG is mainly used in particle form for pharmaceutical applications, such as drug carriers. In this application, the particle shape, size, density and particle size distribution are very important. Since the melting point (T_m) of PEG is not high (around 335 K), milling or grinding is not easy.

In this study, a batch production of particles from PEG with a weight-average molecular weight of 6000 and 10 000 has been performed. PGSS has already been reported for PEG particles from different weight-average molecular weights, 1500, 4000 and 35 000 (Weidner et al., 1996, 2000). However, a detailed engineering approach towards the process is still in its infancy. The experimental results have been presented in terms of particle size, shape, morphology and particle size distribution, which are dependent on the molecular weight, the nozzle diameter and the process conditions. Moreover, flow and solidification models have been applied to study the effect of the rate of nucleation on the particle size and particle size distribution and the effect of different parameters on the particle shape, respectively.

2. Experimental

2.1. Materials

Poly(ethylene glycol)s having a weight average molecular weight (Mw) of 6000 and 10 000 were purchased from Aldrich, The Netherlands. Differential scanning calorimetric (DSC) measurements were carried out to determine the melting point (T_m) and the heat of melting (ΔH_m) of PEG 6000 and 10 000. Table 1 provides the crystallinity of the PEGs calculated using ΔH_m of 100% crystalline PEG (196.8 J/g (Pielichowski and Flejtuch, 2002)). High purity CO_2, 99.99%, was used in the experiments. The materials were used without any further purification treatment.

2.2. Apparatus

A batch set up has been shown schematically in Fig. 1. The set up designed and constructed in our laboratory can withstand a pressure of 25 MPa at 473 K. A cylinder (150 mL), tubes and valves were obtained from Swagelok, The Netherlands. In the set up, the pressure sensor (Dynisco, USA) is mounted in the CO_2 line using a connector just before to the entrance of the cylinder. Before the nozzle, a ball valve (open–close) is used instead of a needle valve as it can be opened more quickly. The cylinder and the tubes are heated using a heating element, whose temperature is controlled using a Eurotherm controller,

Table 1
The physical properties of PEG of different weight-average molecular weights (Mw)

Mw (g/mol)	T_m (K)	ΔH_m (J/g)	Crystallinity, %
6000	332	185.1	94
10 000	338	181.4	92

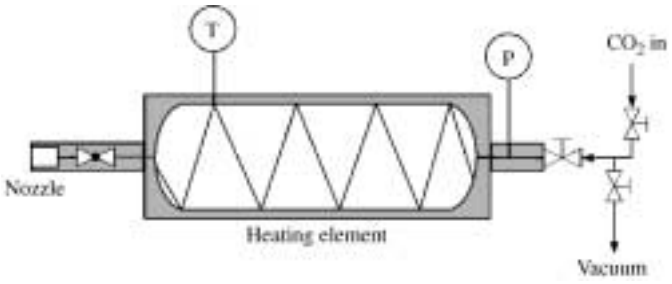

Fig. 1. A schematic drawing of the batch particle production set up.

The Netherlands. The set up is kept hanging on the supports, which oscillate very slowly over 180°. Additionally, an insert having left–right elements in the cylinder also improves the mixing. CO_2 is added using a membrane pump (Lewa, USA) and heated in a double pipe heat exchanger prior to its addition. A drum is used for the expansion of the polymer solution and collection of the particles.

2.3. Experimental method

A known quantity of PEG, ∼ 75 g, was first added to the cylinder and the set up was then subjected to a vacuum. Subsequently, the temperature of the cylinder was set to a desired value and CO_2 was added using a membrane pump to the cylinder until a desired pressure was reached. The set up was then disconnected from the pump and hanged on a horizontal support. The polymer was always allowed to be in contact with CO_2 at least for 3 h despite the fact that the equilibrium, in terms of a pressure reduction, was achieved in a relatively short time. Then, the set up was hung vertical for a few minutes. Before expanding the solution, the CO_2 inlet line was connected to the CO_2 pump to avoid that the pressure inside the cylinder would decrease below the saturation pressure. Finally, the solution was expanded over a nozzle for a short time in a spray drum and solid powder was collected.

2.4. Particle analysis

A wet laser diffraction (WLD) apparatus, Malvern Mastersizer®, was used to measure the particle size and PSD. Toluene was used as a solvent for the particle size measurements. An average particle diameter ($d_{p,0.5}$) is determined from the cumulative volume fraction. The results obtained are an average of several measurements since the mixture, toluene containing suspended particles, was circulated for several times. A scanning electron microscope (SEM) was specifically used to observe the morphology and shape of the particles.

3. Results and discussions

3.1. Literature: CO_2 solubility and viscosity of PEG–CO_2

In PGSS, the shear viscosity plays an important role in the break up of a molten polymer into particles. The higher the

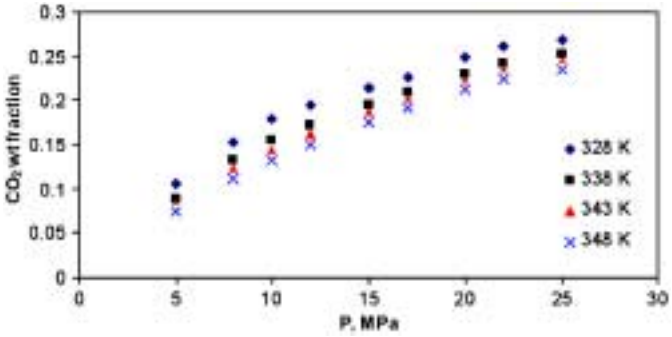

Fig. 2. CO_2 sorption isotherms for PEG 4000.

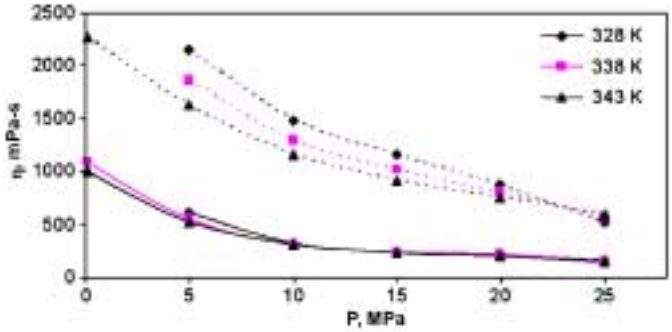

Fig. 3. Viscosity reduction in the presence of CO_2 for PEG 6000 (solid lines) and PEG 10 000 (dotted lines).

viscosity the more difficult is the particle production. Therefore, not only the supersaturation but also the viscosity is important. Since the viscosity reduction due to dissolved CO_2 is dependent on the CO_2 solubility, a detailed knowledge of both is essential.

Weidner et al. (1997) and Wiesmet et al. (2000) have published the CO_2 solubility data for PEGs (Mw 1500–35 000 g/mol) over a pressure range from 0.5–25 MPa at different temperatures in the range of 328–348 K. It was found that the CO_2 solubility is independent of the molecular weights investigated. Fig. 2 shows the CO_2 sorption isotherms of PEG having a molecular weight of 4000. Recently, viscosities of several PEG–CO_2 solutions have been measured by Kukova (2003). The viscosities curves for different molecular weights are shown in Fig. 3. From Fig. 3, it is clear that the viscosity increases considerably with increasing molecular weight.

3.2. Batch experiments

Several experiments have been performed at different temperatures in supercritical states using two different nozzles, 0.81 and 0.36 mm, for PEG 6000 and 10 000. All experimental results of powder generation from PEG 6000 and 10 000 using different diameter nozzles are provided in Table 2. These results have been explained in detail with the help of the various parameters such as the molecular weight, temperature, pressure and nozzle diameter.

Since a few experiments have also been carried out below the melting point of the polymer, it is requisite to ensure that

Table 2
The average diameter ($d_{p,0.5}$) of the particles obtained from PEG 6000 and 10 000 using different nozzles

Mw (g/mol)	d_n (mm)	T (K)	P (MPa)	$d_{p,0.5}$ (μm)
6000	0.81	328	20	297.2
			15	307.2
			12.7	321.0
		338	20	246.9
			15.6	213.7
			12.5	255.1
		343	15.8	324.4
			12.6	316.5
	0.36	328	22	266.9
			13	233.4
		338	22	200.1
			13	198.1
10 000	0.81	328	20.0	318.2
			14.5	330.6
		338	21.1	357.1
			14.8	345.7
		348	20.7	321.1
			15.5	354.8
	0.36	338	21.0	292.7
			12.0	314.2
		348	20.5	309.2
			12.2	280.1

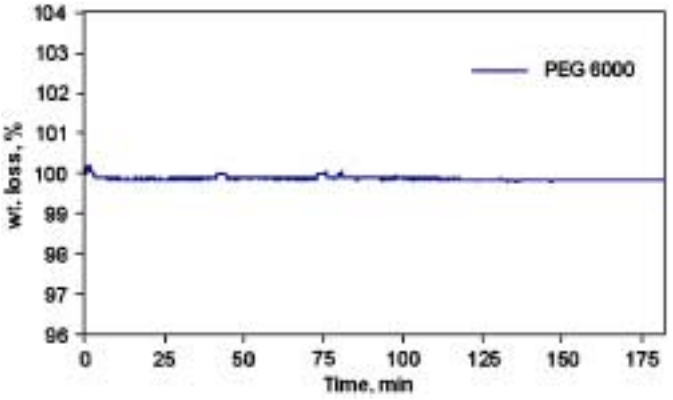

Fig. 4. Weight loss (%) as a function of time of PEG 6000 at 350 K determined using a thermo gravimetric analysis (TGA) apparatus.

PEG is present in the liquid state under these conditions. It has already been reported in literature (Weidner et al., 1997) that the dissolved CO_2 in PEG causes a considerable decrease in the melting point. Minimum CO_2 pressures around 2 and 5.5 MPa at 328 K have been reported for PEG 6000 and 12 000, respectively, above which they are present in the liquid state. Therefore, the pressures above 5.5 MPa have always been selected in the experiments.

During experiments, PEG has always been exposed to the temperatures specified above for a long duration in order to ensure CO_2 saturation. Therefore, a thermal degradation test was performed for the low molecular weight PEG. No weight loss during a thermo gravimetric analysis (TGA) confirms the thermal stability of both PEG (Fig. 4).

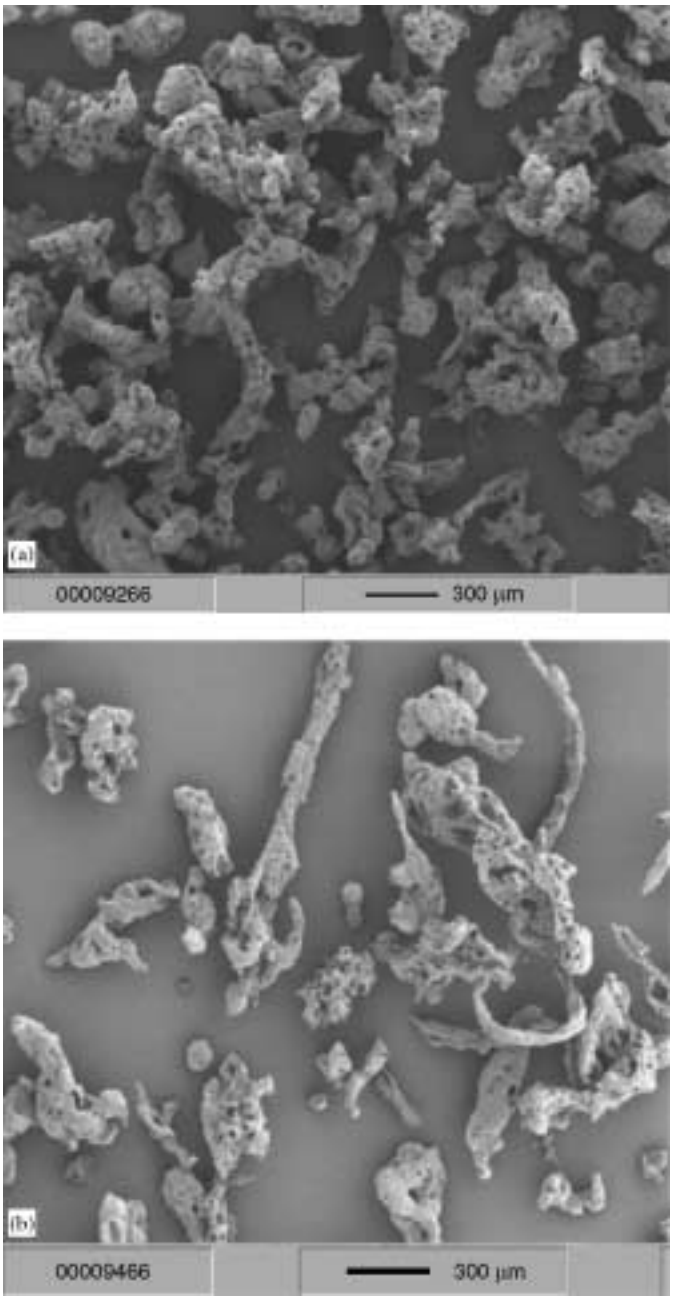

Fig. 5. SEM pictures of the particles obtained using a 0.81 mm diameter nozzle at 20 MPa and 328 K: (a) PEG 6000; and (b) PEG 10 000.

3.2.1. Effect of molecular weight

The shear viscosity of the polymer plays an important role in the PGSS process during the break up of polymer/gas solution into particles. The lower the polymer solution viscosity, the easier is the break up of the solution. The viscosity of polymer can in general be related to its molecular weight, the viscosity increases with increasing molecular weight. Therefore, PEG of different molecular weights have been selected for this study.

The effect of the molecular weight on the shape of the particles for PEG 6000 and 10 000 can be seen in Fig. 5. Relatively long fibre shape particles are obtained for PEG 10 000 compared to PEG 6000 for similar processing conditions below the melting point of both PEG. Since the CO_2 solubility is independent of the molecular weight in case of PEG, the viscosity is mainly responsible for different products. Due to high viscosity, it is more difficult to overcome viscous force in order to break up the solution into smaller particles. Above the melting point (pure polymer), no considerable effect of the molecular weight on the shape of the particles has been found. However, the results can be compared with the particle size as smaller particles have been obtained with the low molecular weight PEG.

3.2.2. Effect of pressure and temperature

The higher the dissolved amount of CO_2 in a polymer, the higher is the supersaturation and hence, a larger nucleation of CO_2 bubbles achieved during the expansion. Since the dissolved amount is a function of temperature and pressure, the effect of temperature and pressure have been discussed together for both PEG. It is possible to produce particles from both PEG 6000 as well as PEG 10 000 even below their melting points. However, an agglomerated mass was obtained along with particles, which is probably due to rapid solidification of the melt. The decrease in the melting point due to dissolved CO_2 allows the expansion of the polymers in the liquid state. The higher the dissolved amount of CO_2, the higher is the decrease in the melting point.

A considerable effect of temperature on the particle size is observed for PEG 6000, Table 2. The particle size increases with increasing temperature above its melting point. The effect can be related to a decrease of the CO_2 solubility with increasing temperature. However, converse to the result above, bigger particles of PEG 6000 are obtained below its melting point probably due to foaming of the particles. In Fig. 6, a large foaming can be seen at the temperature below the melting point for both nozzles in case of PEG 6000. This might be explained by the fact that CO_2 cannot escape easily due to rapid solidification of the particles as the polymer is already below its melting point of pure PEG. Since the solidification is fast, the diffusion of CO_2 from the particles is reduced due to an instantaneous increase in the viscosity of the polymer. Consequently, bubbles of CO_2 are captured inside the particles resulting in foamed particles. The effect of temperature on the particle size is, probably due to high viscosity, absent for PEG 10 000.

A noticeable effect of temperature has also been observed on the shape of the particles. Fig. 7 shows the particles obtained from PEG 6000 and 10 000 under different processing conditions. At high temperatures nearly-spherical shaped particles are obtained. The shape of the particles is mainly dependent on the available solidification time. As the temperature is increased, more sensible heat needs to be removed that delays the solidification process. Moreover, less energy is utilized for evaporation of CO_2 as the amount of CO_2 dissolved decreases with increasing temperature. Such a delayed solidification facilitates retraction of molten polymer into a spherical shape both by visco-elastic relaxation and surface tension.

Unlike temperature, the effect of pressure on the particle size and shape has been absent for both PEG. Similar results have been reported in the literature for PEG of different molecular weights (Weidner et al., 1996). Pressure affects mainly the

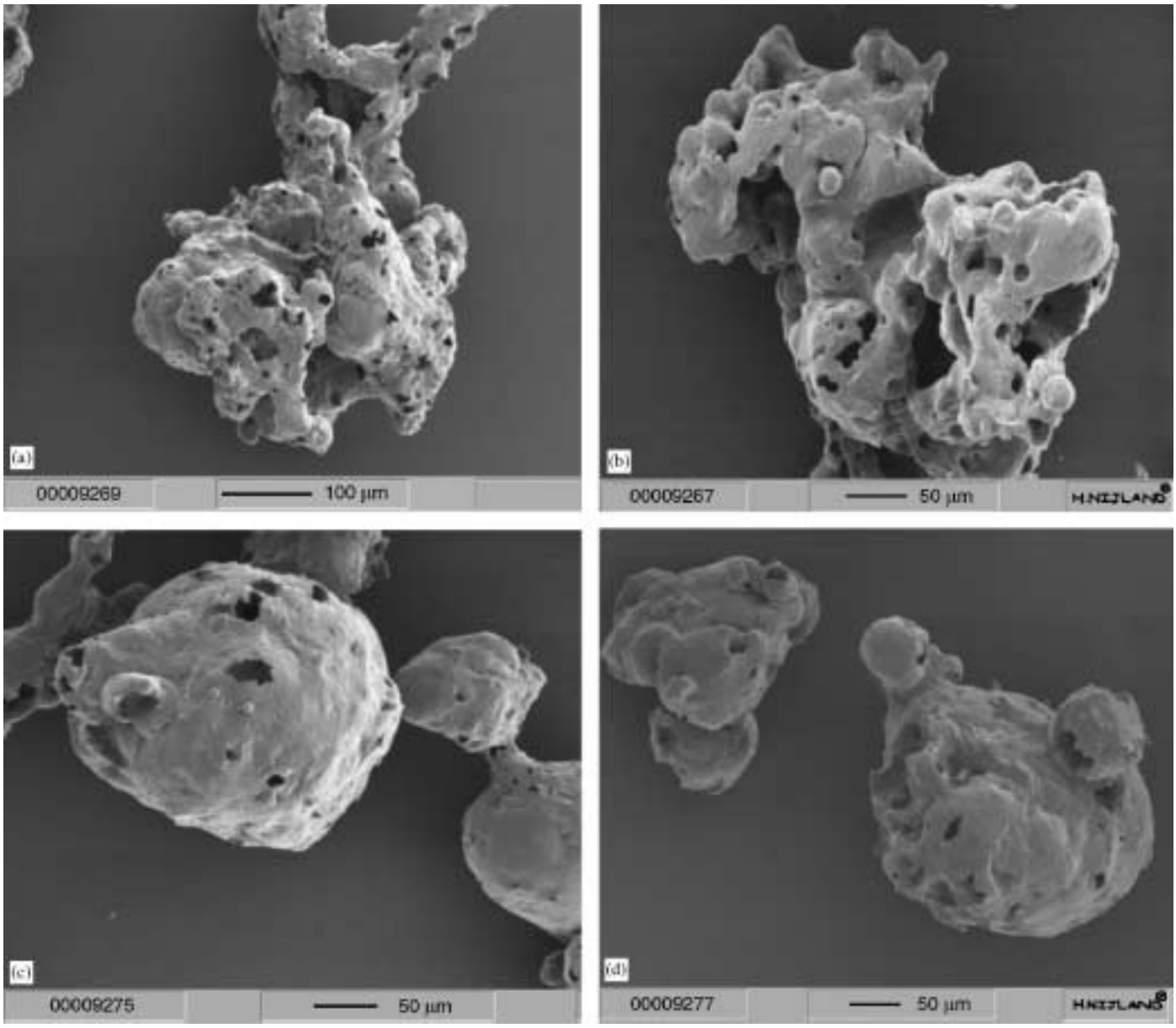

Fig. 6. SEM pictures of the PEG 6000 particles obtained using a 0.81 mm diameter nozzle at: (a) 12.7 MPa, 328 K; (b) 20 MPa, 328 K; (c) 12.5 MPa, 338 K; and (d) 20 MPa, 338 K.

morphology of particles. For example, the bulk densities of the particles obtained at 13 and 22 MPa (338 K) using a 0.36 mm nozzle are 270 and 195 kg/m^3, respectively. The higher the pressure, the higher is the CO_2 solubility. Therefore, more foamed (less dense) particles were produced at the elevated pressures.

In addition to the particle size, shape and morphology, the effect of temperature and pressure on the particle size distribution has also been tested. Fig. 8 shows the particle size distributions of the particles of PEG 6000 and 10 000 obtained under different processing conditions. A bimodal distribution with a very small peak in the range of 0.1–1 μm size is present. In PGSS, generally, a cyclone separator is used in order to remove very fine dust. Such arrangement is not present in our set up. The effect of pressure on the particle size distribution is absent while relatively narrow particle size distributions are obtained at the low temperature for PEG 6000. In case of PEG 10 000, the effect of pressure and temperature on the particle size distribution is clearly absent.

3.2.3. *Effect of nozzle diameter*

From Table 2, it is clear that the average diameter of the particles is decreased with decreasing nozzle diameter. This may be explained using a pressure drop rate depending on the nozzle diameter. The classical homogeneous nucleation theory is not applicable here as it includes only the pressure drop and not the pressure drop rate. The effect of pressure drop rate on the nucleation of CO_2 bubbles has been discussed for a microcellular foaming study by Park et al. (1995). Authors conjectured

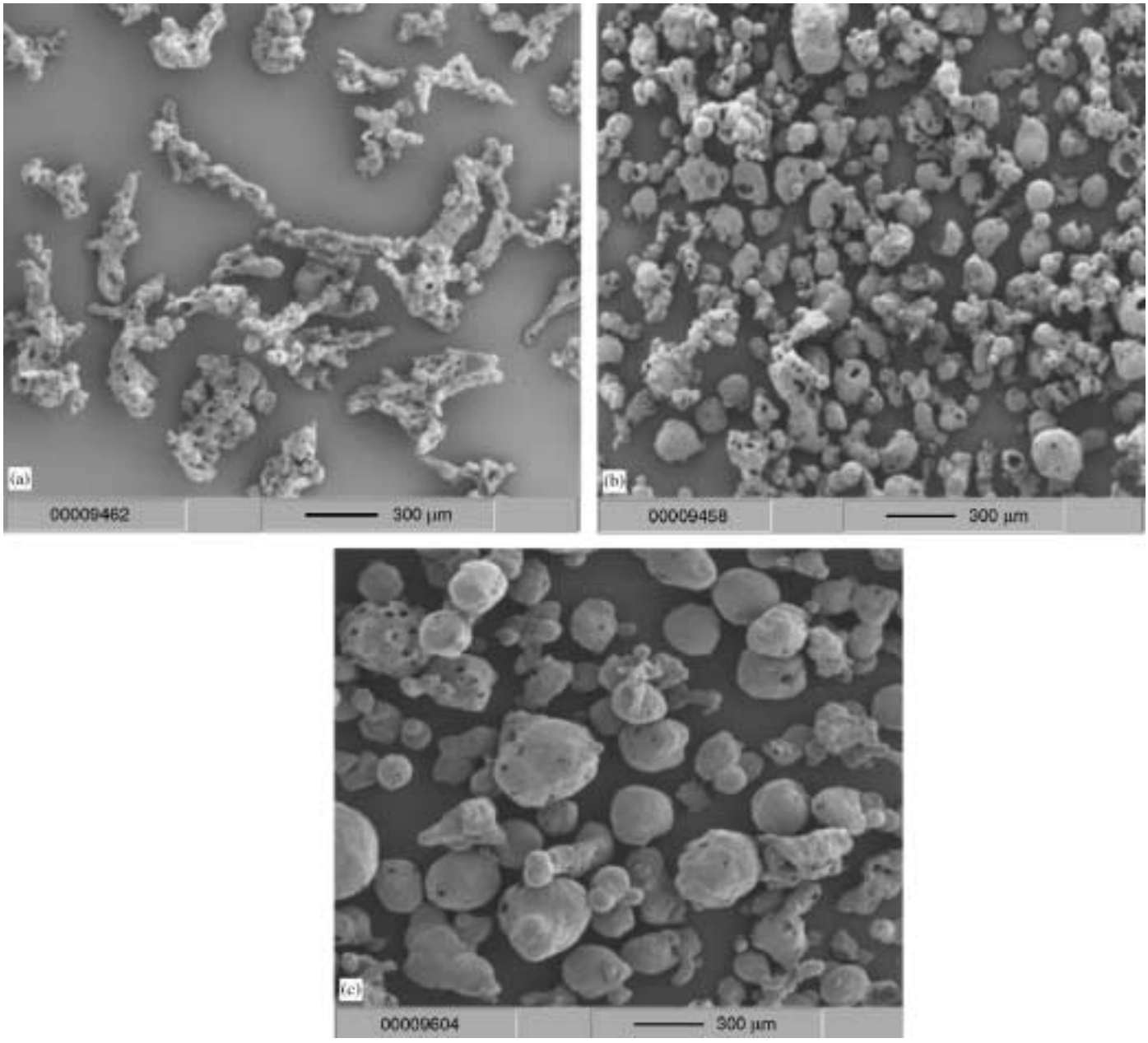

Fig. 7. SEM pictures of the particles: (a) 22 MPa, 328 K, PEG 6000, 0.36 mm nozzle; (b) 22.5 MPa, 338 K, PEG 6000, 0.36 mm nozzle; and (c) 12.2 MPa, 348 K, PEG 10 000, 0.36 mm nozzle.

that a pressure drop rate decides a solubility drop rate, which in turn determines the nucleation rate of CO_2 bubbles. The approach above has been considered also for this study. Thus, it is first necessary to calculate the residence times of a polymer solution in a nozzle under different expansion pressures.

The Fanning equation (1) has been used to calculate the velocity of solution, which in turn was used to calculate the residence time. Here, it has been assumed that the single phase polymer solution is incompressible. The assumption is valid as the concentration of the polymer is always much higher than the concentration of CO_2.

$$\Delta P = 4 f \rho \left(\frac{1}{2}\right) \upsilon^2 \left(\frac{l_n}{d_n}\right). \quad (1)$$

In the equation above, ΔP, f, ρ, υ, l_n, and d_n are the pressure drop, the friction factor, the density of the polymer solution, the velocity of the polymer solution, the length of the nozzle and the diameter of the nozzle, respectively. The density of the polymer solution has been calculated using a linear mixing rule based on the weight fraction of CO_2.

Eq. (1) is applicable to Newtonian fluids. Viscosity measurements have been performed for PEG 6000 at 338 and 343 K in a shear rate range of 10–200 1/s. In this region, the polymer behaves like a Newtonian fluid at both temperatures.

In the equation above, the friction factor is different for laminar to turbulent flow. Therefore, the Reynolds numbers (N_{Re}) have been calculated for different nozzle diameters. Because the velocity is not known, a limiting value of 300 m/s has been

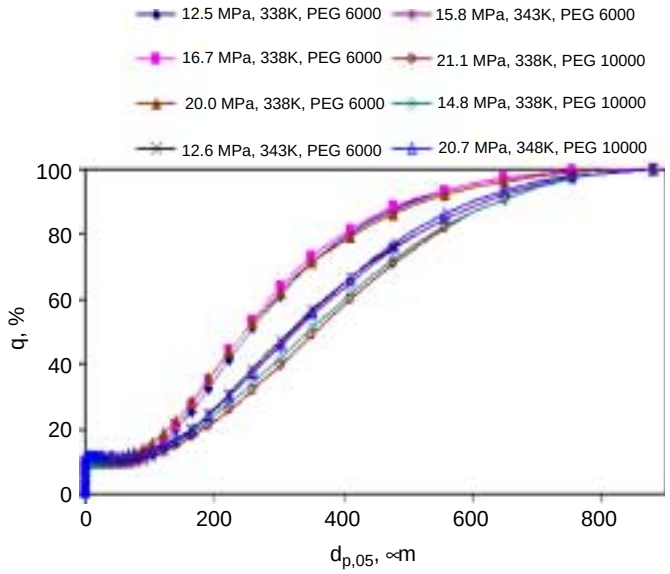

Fig. 8. The particle size distributions of the particles (PEG 6000) obtained using a 0.81 mm diameter nozzle at different processing conditions.

Table 3
The pressure drop rates calculated for different nozzles

P (MPa)	$\frac{\Delta P}{\Delta t}$ (MPa/s) for d_n, 0.36 (mm)	$\frac{\Delta P}{\Delta t}$ (MPa/s) for d_n, 0.81 (mm)
20	26917.74	1100.433
12.5	8467.264	278.7485

used. It has been found that the flows are in the laminar regime (< 2000), despite the high velocity, because of high viscosity of PEG. To calculate the friction factor, the f–N_{Re} relationship for the laminar regime has been used, Eq. (2).

$$4f = 64 * \left(\frac{\eta}{d_n \upsilon \rho}\right) = \frac{64}{N_{Re}}. \quad (2)$$

In Eq. (2), η is the viscosity of the polymer solution. The average pressure drop rate is calculated using Eq. (3), where Δt is the average residence time of the polymer solution.

$$-\frac{\mathrm{d}p}{\mathrm{d}t} \approx -\frac{\Delta P}{\Delta t} \approx -\frac{\Delta P \upsilon}{l_n}. \quad (3)$$

Pressure drop rates obtained using Eqs. (1)–(3) for PEG 6000 are given in Table 3. It is clear from the obtained values that the pressure drop rate is very high in the smaller diameter. An order of magnitude of the pressure drop rate for the smaller nozzle diameter is around 25 times higher than for the bigger nozzle diameter, while it is only around 3 in case of the different pressures for the same nozzle.

Since the CO_2 solubility is linearly proportional to pressure for PEG, the solubility drop rate may be considered proportional to the pressure drop rate. A high solubility drop rate in the smaller diameter nozzle results into a high thermodynamic instability and hence, a large number of nuclei is formed. Moreover, due to a short residence time in the nozzle with a smaller diameter, a growth of the existing nuclei is a limiting factor. A better expansion takes place with this large number of nuclei and hence, smaller diameter particles are produced. On the other hand, a relatively longer time is available for a growth of the existing nuclei in the bigger nozzle. In addition to the particle size, a positive effect of the nozzle diameter on the particle size distribution has been found for PEG 6000, Fig. 9. A narrow particle size distribution is obtained for the smaller diameter nozzle. However, for PEG 10 000, most probably due to high viscosity, an improvement of particle size distribution is not comparable to PEG 6000.

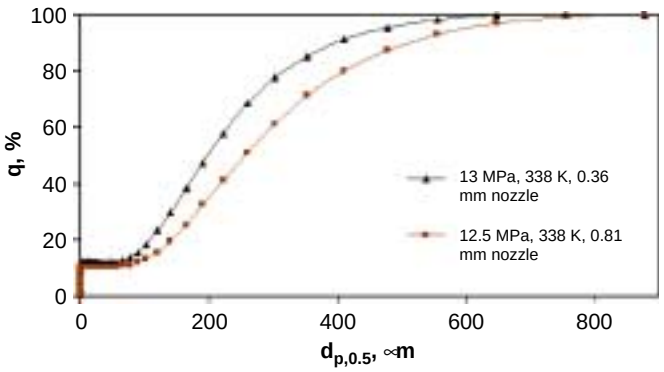

Fig. 9. The particle size distributions of the particles (PEG 6000) obtained using a 0.81 and 0.36 mm diameter nozzle.

3.2.4. Solidification

In PGSS, the effects of temperature and pressure on the shape and morphology can be explained using solidification of molten particles (droplets). The effect of temperature and pressure on the shape and morphology have already been discussed in detail. The amount of CO_2 dissolved, which is dependent on temperature and pressure, also contributes to the solidification in the form of the heat of evaporation (ΔH_v).

A solidification model has been applied to a single droplet. An average time (t_{avg}) required for cooling down the droplet to the melting point with a complete phase change has been calculated using this model. The estimated solidification time provides an insight into the dependency of the particles shape and morphology on different parameters. The assumption used in the model are:

1. The droplet is spherical in shape.
2. The velocity difference between droplet and air present in the spray drum is negligible.
3. CO_2 expansion within the droplet is instantaneous after the nozzle exit.
4. No under cooling of the droplet takes place.
5. The droplet/particle does not shrink or expand during the solidification.

A liquid droplet is cooled by losing heat by CO_2 evaporation and convection to the surrounding. For crystalline material, the latent heat of crystallization (ΔH_m) also needs to be taken into account. According to an energy balance over the droplet,

heat in excess to the evaporation (ΔH_v) must be removed by the convection. Since the convection occurs over a complete solidification period, the average solidification time can be calculated using a convection term. The amount of heat needs to be removed in order to cool the droplet to the melting point of the polymer (T_m) is given by

$$-\rho_p V_p C_p (T_m - T_{\text{mix}}) = hS\Delta T_{\ln} t_{\text{avg}} - \rho_p V_p \Delta H_m + \rho_p V_p \Delta H_v \left(\frac{x_{\text{co}_2}}{1 - x_{\text{co}_2}}\right), \quad (4)$$

where h, S, $\Delta T_{\ln}$, ρ_p, V_p, C_p, T_{mix} and x_{co_2} are the heat transfer coefficient due to convection, the surface area of the droplet, the logarithmic mean temperature difference, density of the polymer, the volume of the droplet (exclusive of the volume of the pores), specific heat of the polymer, the temperature of the mixture and the weight fraction of CO_2, respectively. The $\Delta T_{\ln}$ is calculated using the T_{mix}, T_{air} and T_m. The h is calculated by Eq. (5) proposed by Ranz and Marshall (1952).

$$h = \frac{\lambda_a}{D_d}\left(2.0 + 0.6\sqrt{N_{Re}}\sqrt[3]{N_{Pr}}\right), \quad (5)$$

where λ_a, D_d and N_{Pr} are the thermal conductivity of air, the droplet diameter and the Prandtl number. Before applying the heat balance equation, it is necessary to check the condition that there is no internal temperature gradient present within the droplet (N_{Bi} (Biot number) $\ll 1$) (Bergmann et al., 2000).

For calculations, the properties reported elsewhere for PEG 6000 have been used (Kukova, 2003). The heat of crystallization, the specific heat and the thermal conductivity (λ_p) of PEG 6000 are 181.5 kJ/kg, 2.1–2.5 kJ/kgK (293–393 K) and 0.23 w/mK, respectively. The solidification times have been estimated for the different isothermal conditions used for a nozzle of 0.81 mm. Constant values of $d_{p,0.5}$ as 300 and 320 μm for different pressures at 328 and 338 K, respectively, have been used in the calculations. For porous particles, the volume fraction occupied by the bubbles has been approximated to 0.4 for all calculations. Only a small quantity of powder has been produced during the experiments and hence, a smaller deviation has been present in the temperature of air ($T_{\text{air}} = 296$ K). The results obtained using the model above are shown in Fig. 10.

In Fig. 10, the solidification time is decreased with increasing pressure and decreasing temperature. A high CO_2 solubility is mainly responsible for a decrease in the solidification time. This is related to an amount of energy used for the CO_2 evaporation, which is large at high pressures and low temperatures. At low temperatures, a large amount of CO_2 is captured inside particles due to rapid solidification of particles and hence, porous particles are formed. On the other hand, at high temperatures an amount of sensible heat that needs to be removed from the droplet is increased. Moreover, the heat of evaporation is low due to low CO_2 solubility. Therefore, the solidification is delayed at high temperatures. Thus, more time is available at high temperatures in order to retract molten polymer into a spherical shape.

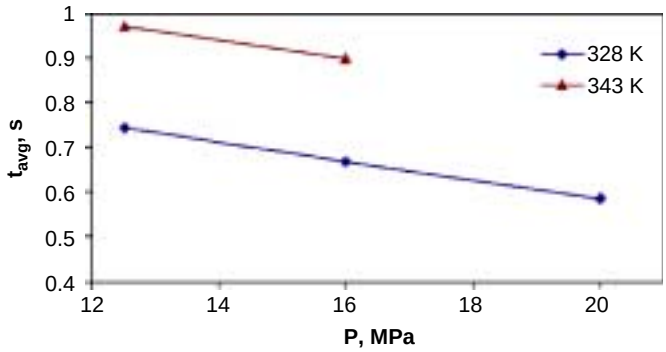

Fig. 10. The estimated average solidification time for PEG 6000 particles at different temperatures.

4. Conclusions

The batch production of particles from PEG of different molecular weights is possible using supercritical CO_2 as a processing solvent. Relatively bigger particles have been produced for PEG 10 000 compared to PEG 6000. The higher the molecular weight the higher is the viscosity of the polymer and hence, the more difficult is the expansion of the high molecular weight polymer melt despite the same CO_2 solubility. The decrease in temperature and the nozzle diameter result into smaller particles. This effect is explained by a large nucleation caused due to high CO_2 solubility and high depressurisation rate (thermodynamic instability). The effect of pressure on the particle size and particle size distribution has been found absent in all PEG. Not only the size but also the shape and the density of the PEG particles can be controlled in the process studied. Depending on the processing conditions, both hollow and dense particles can be produced that can easily be related to high and low CO_2 solubility, respectively. Nearly spherical particles have been produced from PEG 6000 and 10 000 as the temperature has been increased above the melting point. The solidification theory is a good tool to explain the role of temperatures and the CO_2 solubility in determining the shape and morphology of the particles. Finally, a PGSS process provides possibilities of processing various other pharmaceutical and polymeric compounds that are difficult to process by conventional methods.

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